Total Synthesis of the Squalene Synthase Inhibitor Zaragozic Acid C

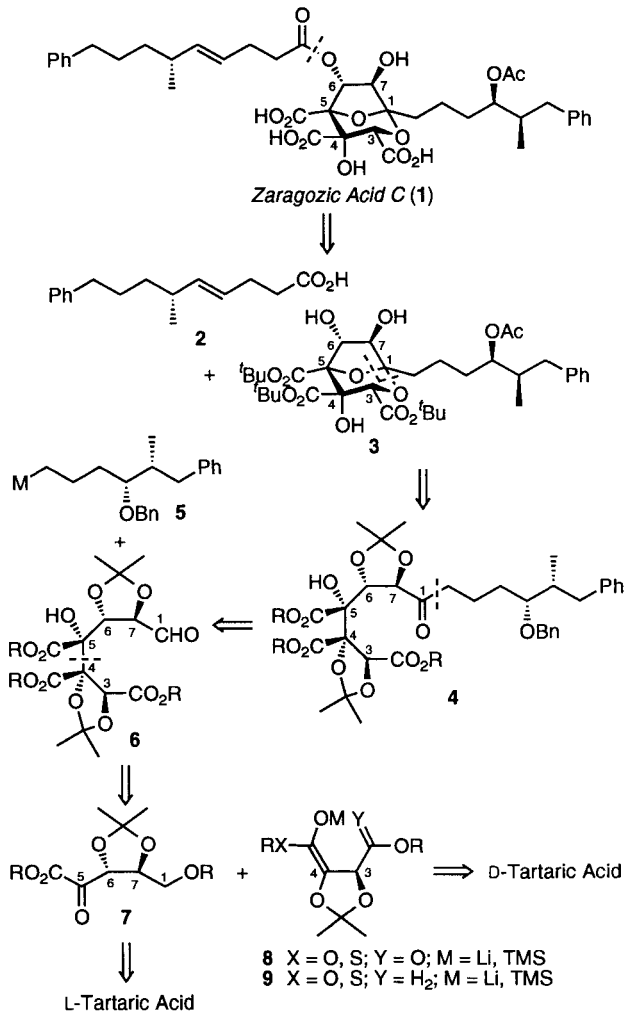
Hiroki Sato,[1] Sei-ichi Nakamura, Nobuhide Watanabe, Shun-ichi Hashimoto*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan
FAX +81(11)706-4981; E-mail hsmt@pharm.hokudai.ac.jp

Received 7 November 1996

Dedicated to Professor E. J. Corey in recognition of his outstanding contributions and leadership in the field of organic synthesis

Abstract: The total synthesis of zaragozic acid C has been achieved by a convergent strategy, wherein the key feature of the construction of 2,8-dioxabicyclo[3.2.1]octane core structure is a simultaneous creation of the C4 and C5 quaternary carbon centers by $Sn(OTf)_2$-promoted aldol coupling reaction between α-keto ester and silyl ketene thioacetal derived from L- and D-tartaric acids, respectively.

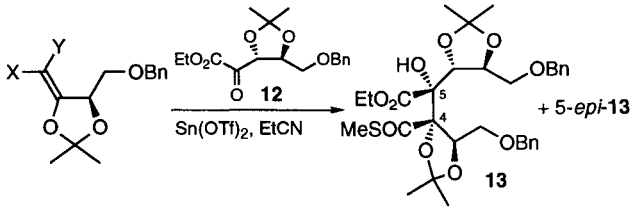
The zaragozic acids[2] and squalestatins,[3] fungal metabolites recently isolated and characterized independently by researchers at Merck and Glaxo respectively, have been shown to be picomolar competitive inhibitors of the enzyme squalene synthase. Consequently, they are regarded as promising lead compounds for the development of new serum cholesterol-lowering drugs. Some members of this family have also been found to display *ras* farnesyl-protein transferase inhibitory activity,[2e,4] which has implication in the development of antitumor agents. Structurally, these molecules share a 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core with an array of six stereogenic centers including contiguous quaternary carbons, and represent considerable variations in the C1 alkyl and C6 acyl side chains. It is therefore not surprising that the zaragozic acids (squalestatins) have elicited considerable attention from numerous synthetic chemists. Of a variety of approaches to the densely oxygenated 2,8-dioxabicyclo[3.2.1]octane ring system by devising innovative strategies and tactics,[5] Nicolaou and co-workers have recently accomplished the total synthesis of zaragozic acid A (squalestatin S1),[6] while efforts of the groups of Carreira[7] and Evans[8] have culminated in the total synthesis of zaragozic acid C (**1**).[9] Herein, we wish to report the alternative, convergent synthesis of **1** highlighting $Sn(OTf)_2$-promoted aldol fragment coupling reaction to join the C4-C5 bond with a simultaneous creation of the contiguous quaternary carbon centers as the key step.



Scheme 1. Retrosynthetic Analysis of Zaragozic Acid C

Our retrosynthetic analysis of zaragozic acid C (**1**) originated from identification of L- and D-tartaric acids in the core structure, which suggested fragment assembly aldol reaction between α-keto ester **7** and enolate **8** or **9** as the key step (Scheme 1).[10] Assessment of the feasibility of introduction of C1 alkyl and C6 acyl side chains as well as internal ketalization would make this strategy highly convergent and efficient, in that the use of protecting groups and oxidation state manipulations could theoretically be minimized.

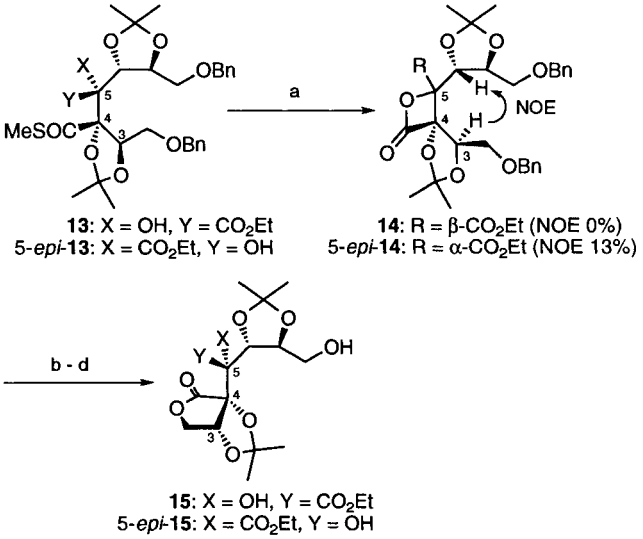
Table 1. $Sn(OTf)_2$-Promoted Aldol Coupling of Silyl Ketene Thioacetal **10** or **11** with α-Keto Ester **12**



silyl ketene thioacetal			temp, °C	time, h	aldol adducts	
	X	Y			yield, %	**13** : 5-*epi*-**13**[a]
10	SMe	OTMS	-70	1.5	90	1 : 2.2
11	OTMS	SMe	-55	1	36	1 : 10

[a] The ratio was determined by ^1H NMR analysis of the crude mixture.

With regard to the aldol reactions associated with our scenario,[11] Kobayashi and co-workers recently reported highly diastereoselective aldol reactions of silyl ketene thioacetals with α-keto esters by employing $Sn(OTf)_2$ or Et_2AlOTf as a promoter, wherein the *syn*:*anti* stereoselectivity was controlled by the geometry of silyl ketene thioacetals.[14] Thus, we decided to apply Kobayashi's protocol to this key reaction. After considerable experimentation,[15] it was found that aldol reaction of (*Z*) silyl ketene thioacetal **10**[16] with α-keto ester **12**,[18] prepared from the D-tartrate and its L-counterpart respectively, in propionitrile in the presence of $Sn(OTf)_2$ at -70 °C proceeded smoothly to give two out of the four possible diastereomers in a 1:2.2 ratio and in a total yield of 90% (Table 1).[20] The stereochemical assignments of each of the easily separable diastereomers followed from ^1H NOE experiments of their derived β-lactones coupled with subsequent



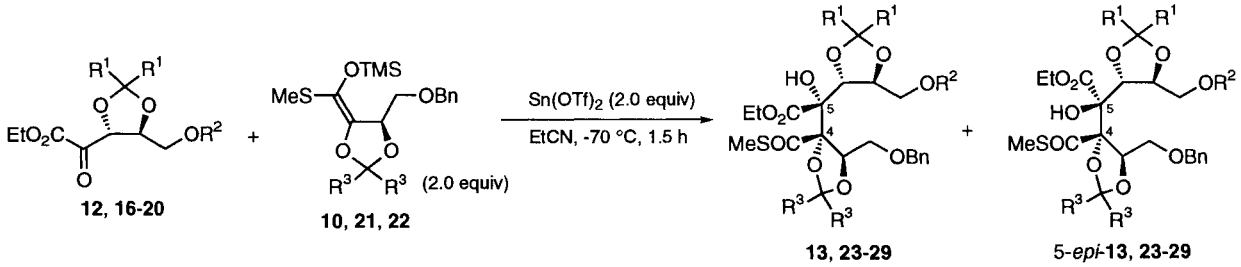
Scheme 2. Stereochemical Assignment of **13** and 5-*epi*-**13**
Reagents and conditions: (a) $Hg(OCOCF_3)_2$, MeCN. (b) K_2CO_3, MeOH. (c) H_2, 10% Pd/C, MeOH. (d) DMAP, MeCN

formation of the γ-lactones (Scheme 2), which established that both of the diastereomers possessed the proper configuration at C4 and the desired isomer **13** was a minor product. On the other hand, the aldol coupling involving (*E*) silyl ketene thioacetal **11**[16] did not take place at -70 °C but proceeded reluctantly at -55 °C to give a complex mixture of products, from which a 1:10 ratio of diastereomers favoring the undesired C5 epimer of **13** was obtained in 36% yield. These results showed that $Sn(OTf)_2$-mediated aldol reactions occurred exclusively on the less hindered *si*-face of silyl ketene acetal **10** or **11** to create the proper configuration at C4, whereas α-keto ester **12** exhibited *si*-facial selectivity, though the magnitude was highly dependent on the geometry of ketene acetals, to disfavor formation of the desired product; (*Z*) silyl ketene thioacetal **10** provided a definite advantage over its (*E*) counterpart **11** in terms of yield and the ratio of the desired product.

Encouraged by a high yield of this reaction coupled with virtually complete diastereofacial selectivity of (*Z*) silyl ketene thioacetal **10**, we sought to improve the stereoselectivity at C5 on the prospect that π-facial selectivity of the carbonyl in α-keto ester might be reversed by judicious choice of protecting groups imparted to each reaction partner.[21] Some representative results are summarized in Table 2, which deserve some comments. While the acetal moiety in α-keto esters showed a little influence on the carbonyl facial selectivity, the ratio of the desired product to the undesired C5 epimer slightly increased with the pentylidene acetal **17** (entry 3 *vs* 1, 2 and 4). With regard to the acetal protection in ketene acetals, exceptionally high order of selectivity for the undesired C5 epimer was obtained with methylene acetal **21**, little variation being observed with isopropylidene and pentylidene acetals **10** and **22** (entry 5 *vs* 3 and 6). Switching protection of the primary alcohol in **17** from benzyl ether to *tert*-butyldiphenylsilyl ether led to the predominant formation of the undesired 5-*epi*-**28** (entry 3 *vs* 7), suggesting that the chelating ability of the oxygen atom might be responsible for the desired π-facial selectivity. Although the positive proof of this was provided by turnover of the product ratio with the synthetically advantageous MEM ether protection, the ratio was 1.6:1 (entry 8). While the mechanistic profile is not clear at present,[14a] these data show that the present fragment assembly aldol reactions are not necessarily nonselective; unfortunately the undesired isomer can be given as a major or sole product, whereas there is great room for improvement in the stereoselectivity favoring the desired product.[22]

Aside from this stereochemical problem, we then proceeded to the elaboration of the target molecule (Scheme 3). The thioester **29**, obtained by taking advantage of the best combination of protecting groups thus far screened for the aldol reaction, was converted to the methyl ester **30** *via* $Hg(OCOCF_3)_2$-mediated methanolysis[24] in 82% yield, which underwent sequential debenzylation, oxidation, and esterification with diazomethane to give the triester **32** in 88% yield. Selective removal of the MEM ether in **32** with TMSCl-NaI[25] was followed by protection of the C5 tertiary alcohol with TMS group *via* two-step bissilylation-monodesilylation sequence to afford the alcohol **34** in 70% yield, which upon Dess-Martin oxidation furnished the

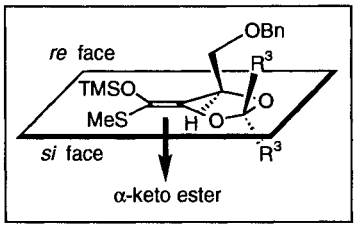
Table 2. $Sn(OTf)_2$-Promoted Aldol Coupling between α-Keto Ester and Silyl Ketene Thioacetal

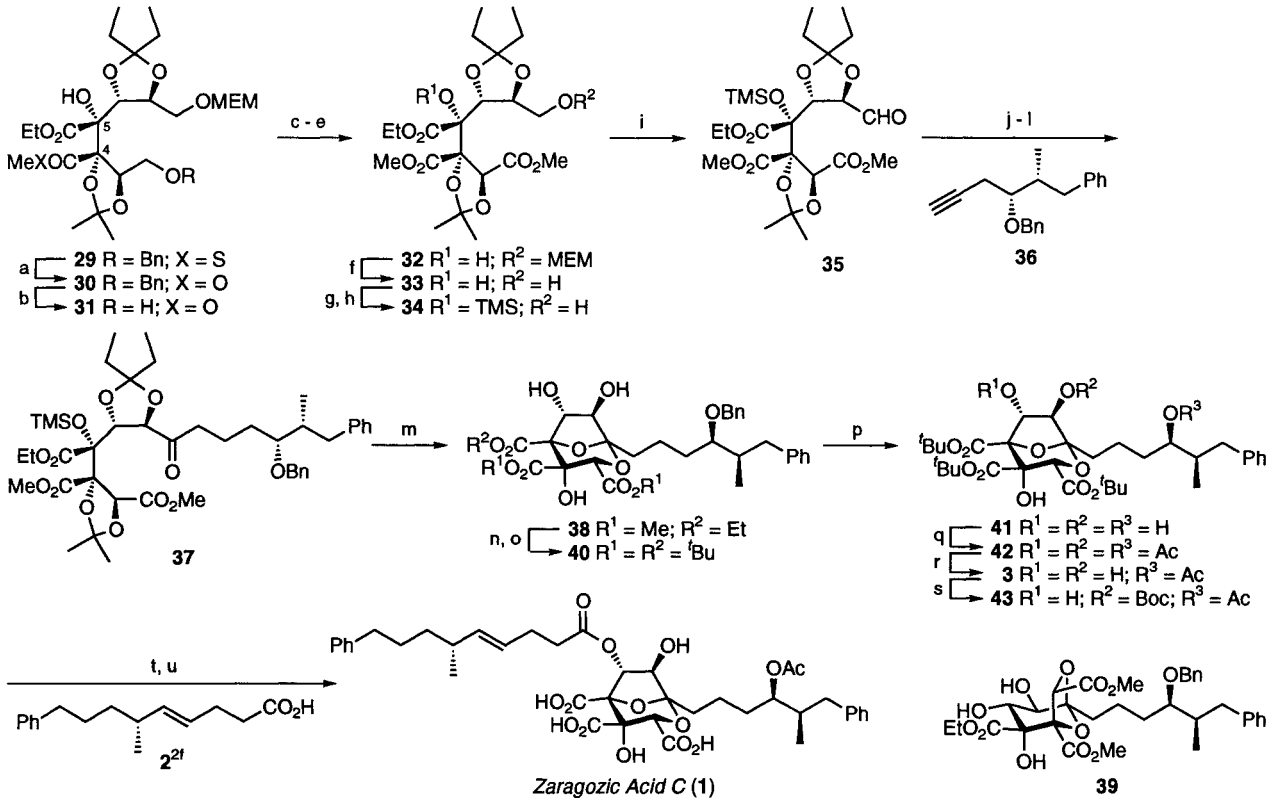


12, 16-20 **10, 21, 22** **13, 23-29** 5-*epi*-**13, 23-29**

entry	α-keto ester			silyl ketene thioacetal		aldol adducts		
		R^1	R^2		R^3		yield, %	ratio[a]
1	**12**	Me	Bn	**10**	Me	**13**	90	1 : 2.2
2	**16**	H	Bn	**10**	Me	**23**	49	1 : 2.6
3	**17**	Et	Bn	**10**	Me	**24**	90	1 : 1.3
4	**18**	*n*-Pr	Bn	**10**	Me	**25**	72	1 : 2.1
5	**17**	Et	Bn	**21**	H	**26**	65	1 : >20
6	**17**	Et	Bn	**22**	Et	**27**	67	1 : 1.9
7	**19**	Et	TBDPS	**10**	Me	**28**	45	1 : 5
8	**20**	Et	MEM	**10**	Me	**29**	83	1.6 : 1

[a] The ratio was determined by ^1H NMR analysis of the crude mixture





Scheme 3. *Reagents and conditions*: (a) $Hg(OCOCF_3)_2$, MeOH, reflux, 4 h, 82%. (b) H_2, 10% Pd/C, MeOH, 17 h. (c) Dess-Martin periodinane, CH_2Cl_2, 1.5 h. (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 5 h. (e) CH_2N_2, Et_2O, 0 °C, 10 min, 88% (4 steps). (f) TMSCl, NaI, MeCN, 0 °C, 1 h, 88%. (g) MeN(TMS)$COCF_3$, 90 °C, 2 h. (h) 10% aq. HCl, Et_2O, 1.5 h, 79% (2 steps). (i) Dess-Martin periodinane, CH_2Cl_2, 1 h, 98%. (j) **36**, *n*-BuLi, THF, -78 °C, 0.5 h, then **35**, -78 °C, 1 h. (k) Dess-Martin periodinane, CH_2Cl_2, 10 h, 79% (2 steps). (l) H_2, 10% Pd/C, AcOEt, 10 min, 87%. (m) 90% aq. TFA, 15 h, 68% of **38** and 7% of **39**. (n) 1N KOH, 1,4-dioxane, reflux, 24 h. (o) *N,N'*-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 24 h, 40% (2 steps). (p) H_2, 10% Pd/C, MeOH, 34 h, 86%. (q) Ac_2O, DMAP, CH_2Cl_2, 0.5 h, 85%. (r) K_2CO_3, MeOH, 1 h, 91%. (s) $(Boc)_2O$, 4-pyrrolidinopyridine, Et_3N, CH_2Cl_2, 0 °C, 12 h, 71%. (t) **2**, DCC, DMAP, CH_2Cl_2, 48 h, 85%. (u) TFA, CH_2Cl_2, 16 h, quant.

aldehyde **35** in 98% yield, with no sign of α-epimerization next to the aldehyde. Installation of the C1 alkyl appendage was uneventfully achieved by addition of the lithium acetylide derived from **36**[26] to **35**, whereas addition of the corresponding alkyllithium or the Grignard reagent afforded a complex mixture of products due probably to the attack on the ester functionality. Subsequent oxidation followed by catalytic hydrogenation of a triple bond furnished the ketone **37** in 69% overall yield from **35**. Crucial internal ketalization *via* removal of the TMS and acetal groups was performed by exposure of **37** to 90% aqueous TFA to afford the bicyclic core **38** in 68% yield, along with 7% of the structural isomer **39**. Since we could not observe equilibration between **38** and **39** under the present reaction conditions, predominant formation of **38** *via* attack of the rapidly deprotected C5 hydroxy group on the carbonyl might be ascribed to more facile deprotection of C6,C7 pentylidene acetal than hydrolysis of C3,C4 isopropylidene acetal as monitored by TLC analysis.[5p,9b] Saponification of **38** and subsequent esterification with *N,N'*-diisopropyl-*O*-*tert*-butylisourea[2f,27] afforded the tris(*tert*-butyl) ester **40** in 40% yield. Hydrogenolysis of the C4' benzyl ether and subsequent peracetylation produced the triacetate **42** in 73% yield, which intersected Carreira's synthesis of zaragozic acid C.[7,28] Thus, completion of the synthesis was uneventfully accomplished according to the felicitous method of Carreira.[7b] The synthetic material **1**, $[\alpha]_D^{23}$ +9.4° (*c* 0.30, EtOH) [lit.,[2b] $[\alpha]_D^{20}$ +9.6° (*c* 0.29, EtOH)], obtained as a colorless amorphous solid exhibited identical spectroscopic data with those reported for natural zaragozic acid C (IR, ^1H NMR, ^{13}C NMR, HRMS).[2b]

In summary, we have achieved the total synthesis of zaragozic acid C in a highly convergent manner. Efforts directed at improving the stereoselectivity of a key fragment assembly aldol process as well as a second-generation synthesis of zaragozic acids are currently underway.

Acknowledgement. This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture and also by the Special Coordination Funds of the Science and Technology Agency of the Japanese Government.

References and Notes

(1) Visiting scientist from Zeria Pharmaceutical Co., Ltd., Saitama 360-01, Japan.

(2) (a) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151. (b) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221. (c) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Nallin Omstead, M.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 80. (d) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. *Tetrahedron Lett.* **1993**, *34*, 399. (e) Dufresne, C.; Wilson, K. E.; Singh, S. B.; Zink, D. L.;

Bergstrom, J. D.; Rew, D.; Polishook, J. D.; Meinz, M.; Huang, L.; Silverman, K. C.; Lingham, R. B.; Mojena, M.; Cascales, C.; Pelaez, F.; Gibbs, J. B. *J. Nat. Prod.* **1993**, *56*, 1923. (f) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261.

(3) (a) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639. (b) Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P. A.; Watson, N. S. *J. Antibiot.* **1992**, *45*, 648. (c) Blows, W. M.; Foster, G.; Lane, S. J.; Noble, D.; Piercey, J. E.; Sidebottom, P. J.; Webb, G. *J. Antibiot.* **1994**, *47*, 740.

(4) Gibbs, J. B.; Pompliano, D. L.; Mosser, S. D.; Rands, E.; Lingham, R. B.; Singh, S. B.; Scolnick, E. M.; Kohl, N. E.; Oliff, A. *J. Biol. Chem.* **1993**, *268*, 7617.

(5) (a) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1839. (b) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Sidebottom, P. J.; Sik, V.; Watson, N. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1841. (c) Aggarwal, V. K.; Wang, M. F.; Zaparucha, A. *J. Chem. Soc., Chem. Commun.* **1994**, 87. (d) McVinish, L. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 923. (e) Gable, R. W.; McVinish, L. M.; Rizzacasa, M. A. *Aust. J. Chem.* **1994**, *47*, 1537. (f) Abdel-Rahman, H.; Adams, J. P.; Boyes, A. L.; Kelly, M. J.; Lamont, R. B.; Mansfield, D. J.; Procopiou, P. A.; Roberts, S. M.; Slee, D. H.; Watson, N. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1259. (g) Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; De Riccardis, F.; Nadin, A.; Leresche, J. E.; La Greca, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2184. (h) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; La Greca, S.; Tsuri, T.; Yue, E. W.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2187. (i) Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185. (j) Kraus, G. A.; Maeda, H. *J. Org. Chem.* **1995**, *60*, 2. (k) Caron, S.; McDonald, A. I.; Heathcock, C. H. *J. Org. Chem.* **1995**, *60*, 2780. (l) Gurjar, M. K.; Das, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **1995**, *36*, 1933, 1937. (m) Schlessinger, R. H.; Wu, X.-H.; Pettus, T. R. R. *Synlett* **1995**, 536. (n) Armstrong, A.; Barsanti, P. A. *Synlett* **1995**, 903. (o) Shimizu, A.; Ohmori, K.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Carbohydr. Lett.* **1996**, *1*, 433. (p) Hodgson, D. M.; Bailey, J. M.; Harrison, T. *Tetrahedron Lett.* **1996**, *37*, 4623. (q) Maezaki, N.; Gijsen, H. J. M.; Sun, L.-Q.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 6685. (r) Tsubuki, M.; Tomitsuka, K.; Okita, H.; Honda, T. *Symposium Papers of 38th Symposium on the Chemistry of Natural Products*; Sendai, Japan, 1996; pp 601.

(6) (a) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2190. (b) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467.

(7) (a) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825. (b) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

(8) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111.

(9) For reviews, see: (a) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 773. (b) Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622.

(10) A similar approach based on disconnection at the C4-C5 bond has already been adopted by Evans and co-workers, culminating in a remarkably elegant and efficient synthesis of zaragozic acid C.[8] Their success might be attributed to an indirect tactics in the construction of the C5 stereogenic center *via* aldol coupling with aldehyde followed by oxidation and diastereoselective addition of vinylmagnesium bromide as the latent carboxyl functionality.

(11) Attempts at aldol coupling between the lithium or titanium[12] enolate derived from dimethyl D-tartrate acetonide and α-keto ester patterned after Seebach's enolate chemistry[13] met with little success. A similar investigation with acetylacetone but not with α-keto esters has been undertaken by Aggarwal and his co-workers.[5c]

(12) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722.

(13) Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030.

(14) (a) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1324. (b) Kobayashi, S.; Horibe, M. *Synlett* **1993**, 855.

(15) We could not obtain the silyl ketene thioacetal with the ester functionality in place of the benzyloxymethyl group in **10** with synthetically useful levels of purity and yield, so that the $Sn(OTf)_2$-mediated aldol coupling was not explored. In this regard, it is also worthy of note that neither of the corresponding silyl ketene acetals proved to be stable enough to be prepared.

(16) (*Z*) Silyl ketene thioacetal **10** and its (*E*) isomer **11** were prepared with virtually complete stereoselectivity (>98:2) by enolization of the corresponding thioester, prepared from (2*S*,3*R*)-4-(benzyloxy)-2,3-(dimethylmethylenedioxy)butanal[17] by the three-step sequence [(1) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (2) $(COCl)_2$, DMF, CH_2Cl_2; (3) NaSMe, *n*-Bu_4NI, CH_2Cl_2, 0 °C], in THF at -78 °C with LiHMDS and KHMDS, respectively, followed by addition of TMSCl. It was found that **10** and **11** originated from the kinetic and thermodynamic enolates, respectively. The stereochemical assignments were established due to the observation of ^1H NOE (0.3%) between $Si(CH_3)_3$ and methine proton in **10**, whereas the corresponding signal enhancement was not observed with **11**.

(17) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929.

(18) The α-keto ester **12** was prepared from (2*R*,3*S*)-4-(benzyloxy)-2,3-(dimethylmethylenedioxy)butanal[17] *via* the α-keto vinyl ether intermediate[19] by the following five-step sequence: (1) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (2) $(COCl)_2$, DMF, CH_2Cl_2; (3) MeONHMe-HCl, pyridine, CH_2Cl_2; (4) ethyl vinyl ether, *t*-BuLi, THF, -78 °C; (5) O_3, CH_2Cl_2, -78 °C, then Me_2S.

(19) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913.

(20) Neither aluminum triflates nor typical Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, and $SnCl_4$ were found to be effective for the present aldol coupling.

(21) These isomers were readily distinguishable by ^1H NMR signals for the *S*-methyl protons, which were always 0.04-0.1 ppm downfield in the desired product relative to its C5 epimer.

(22) Attempts to improve the stereoselectivity *via* a triple asymmetric induction using $Sn(OTf)_2$ coordinated with a chiral diamine[23] failed, simply because the reaction did not work.

(23) Mukaiyama, T.; Kobayashi, S. In *Stereocontrolled Organic Synthesis*, Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, 1994; p 37.

(24) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515.

(25) Rigby, J. H.; Wilson, J. Z. *Tetrahedron Lett.* **1984**, *25*, 1429.

(26) The synthesis of alkyne **36** will be reported in a full account.

(27) Mathias, L. J. *Synthesis* **1979**, 561.

(28) Specific rotation of the compound **42** was inconsistent with the reported value.[7b] The observed rotation: $[\alpha]_D^{21}$ +17.6° (*c* 0.91, CH_2Cl_2) [lit.,[7b] $[\alpha]_D$ +69.9° (*c* 0.29, CH_2Cl_2)].